

1 **Genetic Evaluation of Cardiomyopathy - A Heart Failure Society of America**

2 **Practice Guideline**

3 **Short Title:** Genetic Evaluation of Cardiomyopathy

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36

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43

44 **Abstract**

45

46 This guideline describes the approach and expertise needed for the genetic evaluation of
47 cardiomyopathy. First published in 2009 by the Heart Failure Society of America (HFSA), this
48 guidance has now been updated in collaboration with the American College of Medical Genetics
49 and Genomics (ACMG). The writing group, composed of cardiologists and genetics
50 professionals with expertise in adult and pediatric cardiomyopathy, reflects the emergence and
51 increased clinical activity devoted to cardiovascular genetic medicine. The genetic evaluation of
52 cardiomyopathy is a rapidly emerging key clinical priority, as high throughput sequencing is now
53 feasible for clinical testing, and conventional interventions can improve survival, reduce
54 morbidity, and enhance quality of life. Moreover, specific interventions may be guided by genetic
55 analysis. A systematic approach is recommended: always a comprehensive family history; an
56 expert phenotypic evaluation of the proband and at-risk family members to confirm a diagnosis
57 and guide genetic test selection and interpretation; referral to expert centers as needed; genetic
58 testing, with pre- and post-test genetic counseling; and specific guidance as indicated for drug
59 and device therapies. The evaluation of infants and children demands special expertise. The
60 approach to manage secondary and incidental sequence findings as recommended by the
61 ACMG is provided.

62

63

64 **Key Words:** cardiomyopathy; genetics; genetic analysis; practice guideline; secondary
65 findings.

66 **Introduction**

67 Continued rapid progress has been made in understanding the genetic basis of
68 cardiomyopathy. This work, which describes the content, approach and expertise needed for a
69 cardiomyopathy genetic evaluation, was first developed in a guideline statement in 2008 and
70 published in 2009 for the Heart Failure Society of America (HFSA).¹ This has now been updated
71 by a writing group organized with the American College of Medical Genetics and Genomics
72 (ACMG) and the HFSA to serve as a practice resource (ACMG) and as a revised guideline
73 statement (HFSA).

74 This collaboration of cardiovascular and genetics professionals mirrors a recent
75 proliferation of specialized cardiovascular genetics clinics.² Most commonly cardiologists, adult
76 or pediatric, with special interest or training in cardiovascular genetics, team up with genetics
77 professionals, usually board-eligible or board-certified genetic counselors and/or clinical
78 geneticists, ideally with cardiovascular expertise, to provide state-of-the-art genetics services to
79 the many patients and families with cardiomyopathy. This growth has been triggered by
80 improvements in technology for clinical genetic testing, resulting in the availability of large
81 clinical genetic testing panels, where numerous genes of interest can be sequenced quickly,
82 efficiently and accurately using continually developing massively parallel DNA sequencing
83 technologies. This growth also recognizes the critical importance of integrated expert
84 phenotypic information with final clinical recommendations in light of burgeoning sequence
85 information.³

86 This collaboration also speaks to the recent prominence of cardiovascular genetics and
87 genomics brought about by the emergence of clinical exome sequencing and the ACMG
88 recommendation, first in 2013⁴ and updated in 2016,⁵ to return relevant and actionable
89 secondary findings. Of the 59 medically actionable genes cited in 2016, 30 (51%) had
90 cardiovascular phenotypes, and 16 (27%) were genes that included cardiomyopathy

91 phenotypes. By request from the ACMG, we also provide guidance for secondary findings
92 derived from cardiomyopathy genes.

93 The rationale for the inclusion of cardiomyopathy genes in the ACMG secondary findings
94 list, and the basis for the clinical screening, counseling and molecular recommendations
95 contained herein, are because the cardiomyopathies are medically actionable: well established
96 treatments or interventions are available to improve survival, reduce morbidity, and enhance
97 quality of life.^{6, 7} Cardiomyopathies may present late in their course with advanced disease,
98 which includes heart failure, heart block and/or life-threatening arrhythmias including sudden
99 cardiac death, and thromboembolic events, including stroke from atrial arrhythmias or
100 ventricular thrombus. Thus, the rationale to identify genetic risk is compelling, so that those
101 found to be at-risk can undergo interval screening to detect the earliest manifestations of the
102 cardiomyopathy phenotype. The first evidence of a phenotype then permits earlier
103 interventions,⁷ including lifestyle modifications, drugs to slow or halt disease progression or to
104 prevent thromboembolism, and procedures, drugs or devices to reduce the risk of sudden
105 cardiac death.⁶ Identification of at-risk individuals, whether affected but asymptomatic or those
106 clinically unaffected may also have implications for genetic counseling and reproductive
107 decision-making.

108 Cardiovascular physicians are expert at assessing the nuances of cardiomyopathy
109 phenotypes or sub-phenotypes, an essential contribution to cardiovascular genetics care. As in
110 2009,¹ our current approach continues to be stratified by cardiomyopathy phenotype, as clinical
111 and genetic data collection, analysis and decision making for the cardiomyopathies remain
112 anchored by phenotypic categories.

113 ***The Family as the Unit of Care***

114 A critical transition for cardiovascular practitioners who wish to more fully actualize
115 cardiovascular genetic medicine is to adopt the family as the unit of care, a concept inherently
116 understood by genetics professionals. For cardiovascular providers, moving the care paradigm

117 beyond the patient (proband), who often presents with a fully developed phenotype and at times
118 with advanced life-threatening disease, to at-risk relatives is mandatory to fulfill the promises of
119 precision medicine. Moreover, collaboration with and care for the family unit is an essential
120 component of the genetic evaluation. This includes establishing a genetic etiology for the
121 proband and affected family members, the clinical evaluation of at-risk family members,
122 cascade genetic testing of family members as indicated, and genetic counseling at all steps. All
123 of this will not only augment the evidence of variant pathogenicity but also will provide insight
124 into penetrance, age of onset, pleiotropy and disease expression.

125 Ideally family-based cardiovascular genetic medicine also means developing integrated
126 teams with pediatric and adult training and expertise that are able to provide coordinated care
127 across all age groups. Identification of disease and pathogenic variants in an adult parent
128 facilitates testing and potential treatment of pediatric-aged children. Conversely, if the index
129 case is a child, the testing and treatment of adult-aged relatives may also be needed. Thus, we
130 recognize the critical need to address accessible delivery of care of the family across all ages.
131 This also includes managing insurance coverage for the evaluation of asymptomatic relatives
132 based on their family history.

133 Genetic cardiomyopathy has substantial complexity, as shown by overlap in phenotype
134 as well as an overlap of genes.⁸ Despite this complex interplay of genes, variants and
135 phenotypes, current knowledge when combined with expert phenotyping and the sensitivity and
136 specificity of current genetic testing, is sufficient to effectively conduct genetic cardiomyopathy
137 evaluations. We caution, however, that variant interpretation must be thoughtful, rigorous and
138 leverage the most up-to-date approaches, as not all variants identified by genetic testing will be
139 clinically significant or disease-causing. Key resources include use of the most recent
140 ACMG/AMP guidance,^{5,9} now being augmented by ClinGen, a National Human Genome
141 Research Institute-sponsored initiative to curate genes and variants and place them into

142 ClinVar, a publically accessible database,^{10, 11} and other large publicly accessible reference
143 databases.

144 ***Types of Cardiomyopathy***

145 The genetic basis of hypertrophic cardiomyopathy (HCM) is well established, largely a
146 disease caused by mutations in genes encoding sarcomeric proteins. That familial dilated
147 cardiomyopathy (DCM) has a genetic basis is also well accepted. By DCM, we clarify that the
148 DCM term herein is used in place of the more technical attribution “idiopathic dilated
149 cardiomyopathy,” where the other common and easily clinically detected causes of systolic
150 dysfunction such as coronary artery disease, primary valvular or congenital heart disease, or
151 prior exposure to cancer chemotherapy or other injurious drugs, have been excluded. However,
152 the preponderance of DCM occurs without apparent familial disease, and whether non-familial
153 DCM is principally a genetic condition remains uncertain.^{8, 12, 13} The much greater numbers of
154 genes and the diversity of variants identified (allelic and locus heterogeneity) with DCM is more
155 extensive relative to the other cardiomyopathies,^{8, 12, 14, 15} making genetic testing inherently more
156 challenging. Arrhythmogenic right ventricular cardiomyopathy (ARVC), which is much less
157 common than HCM or DCM, also has a well-established genetic basis associated with
158 mutations in genes that encoded desmosomal elements. Restrictive cardiomyopathy (RCM),
159 although quite rare, also shares in part a genetic basis with HCM.

160 In contrast to HCM, DCM, RCM and ARVC, the left ventricular non-compaction (LVNC)
161 phenotype remains enigmatic and without consensus as to whether it should be considered a
162 primary cardiomyopathy,¹³ a variant morphologic trait¹⁶ or something else.^{17, 18} We favor
163 describing it as a phenotype because an increasing body of population-derived high-quality
164 imaging evidence, not available when LVNC was deemed a primary cardiomyopathy,¹³ now
165 shows that increased ratios of non-compacted (trabeculated) to compacted (non-trabeculated)
166 myocardium may be present in 2-10% or more of the population depending on the definition and
167 test sensitivity.^{16, 19, 20} Further, studies in highly trained athletes^{21, 22} and pregnancy,²³ suggest

168 LVNC may progress and regress, akin to ventricular remodeling and reverse remodeling.
169 Therefore, LVNC has been included and referred to as a non-compaction phenotype rather than
170 a unique form of cardiomyopathy. Additional background is provided in the online supplement.

171

172 **Approaches to Review and Publication by the ACMG and HFSA**

173 The writing group was established conjointly with the ACMG and HFSA between 2013
174 and 2015. The approaches to creating, curating and approving practice guidelines or practice
175 resources for the HFSA and ACMG, respectively, have been outlined in each publication. The
176 material covered in this and the companion document²⁴ are congruent with one another.

177 Differences in scope, including supplemental materials, are denoted and cross-referenced.

178 The writing group was comprised of a panel of experts, board certified cardiologists and
179 genetics professionals with experience and expertise in genetic cardiomyopathies
180 (Supplemental Table XX), with a goal to revise a prior HFSA publication in a conjoint effort with
181 a new document for the ACMG. Each author was screened for relevant conflicts of interest and
182 all conflicts shown were considered non-substantial to influence the document. Dr. Vatta was
183 included in the writing group prior to his employment with a for-profit genetic testing company;
184 following his employment potential conflicts of interest regarding genetic testing indications were
185 managed by his recusal from pertinent discussions.

186

187 **Use of Medical Evidence in this Guideline**

188 We address two questions here. The first question is that of clinical validity: “Does the
189 evaluation or test correlate with the outcome of interest?”²⁵ Since randomized clinical trials
190 evaluating the clinical accuracy of diagnosis with or without a genetic evaluation or genetic
191 testing are not generally feasible, as in the prior guideline¹ we have used a different format for
192 level of evidence. By genetic evaluation we mean a systematic approach that includes a
193 comprehensive family history, phenotypic evaluation of the proband and at-risk family members,

194 genetic counseling, genetic testing, if indicated, with pre- and post-test genetic counseling, and
195 guidance as indicated for specific drug and/or device, or other specific therapeutic interventions.
196 By genetic testing we mean DNA sequencing or other DNA testing modalities to identify DNA
197 variants relevant for the phenotype of interest. **Level A:** Genetic evaluation and testing has a
198 high correlation with the cardiomyopathic disease of interest in studies with a moderate or large
199 sample size; **Level B:** Genetic evaluation and testing has a high correlation with the
200 cardiomyopathic disease of interest in smaller or single center studies; and **Level C:** Genetic
201 evaluation and testing correlates with the cardiomyopathic disease of interest in case reports.
202 All levels were assigned based upon literature review and full consensus of the writing group.

203 The second question is one of clinical effectiveness: “Does performing a genetic
204 evaluation or test result in improved patient outcomes?” This question depends also on the
205 multiple treatment options that follow from a firm genetic and phenotypic diagnosis in
206 cardiomyopathy, as well as the perceived clinical utility, which in this context is the benefit of
207 those who receive a genetic evaluation or test. Again, randomized studies to address this
208 question controlling for genetic diagnosis are not feasible. Moreover, consensus on how to
209 appropriately measure the impact of genetic evaluation and testing on personal utility of patients
210 is still developing,²⁶ while the impact of genetic evaluation and testing on societal utility is a
211 broader question beyond our current scope. Therefore, while acknowledging these constraints,
212 we have interpreted the level of evidence within the existing HFSA framework,²⁷ and have
213 based the strength of recommendations on this level, as well as on our current knowledge of
214 clinical effectiveness from the totality of information currently available.

215 While we recognize that essentially no randomized controlled clinical trials have been
216 conducted to support most of the recommendations herein, this also provides an opportunity to
217 press our constituencies to design and conduct innovative and rigorous research studies to
218 achieve a substantive evidentiary basis for these guidelines. While the present guidance may be

219 considered “expert” it is well known that well designed and rigorously performed clinical studies
 220 have routinely shown that “conventional wisdom” may be simply wrong.

221

222 **Guideline 1. Obtaining a family history of at least three generations, including the**
 223 **creation of a pedigree, is recommended for all patients with a primary**
 224 **cardiomyopathy.**

225	Cardiomyopathy Phenotype	Level of Evidence
226	Hypertrophic cardiomyopathy (HCM)	A
227	Dilated cardiomyopathy (DCM)	A
228	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	A
229	Restrictive cardiomyopathy (RCM)	A
230	Cardiomyopathies with extra-cardiac manifestations	A
231	Left ventricular non-compaction (LVNC)	see background

232

233 **Key Points:** A genetics professional is skilled at obtaining a reliable family history and
 234 identifying those at risk, which is critically important once genetic results have been obtained.
 235 Specific questions should be focused to elicit possible affected relatives that may not be
 236 identified in a general family history. Primary clinical data should be reviewed, whenever
 237 possible, and may require collection of relatives’ records or post mortem reports. These latter
 238 may include relevant prenatal (including fetal loss), infant, pediatric, or adult records.

239

240 **Guideline 1 - Background.**

241 The family history, a key component of any medical and genetic evaluation, is
 242 particularly relevant for the cardiomyopathies. The goals of a family history are to ascertain if the
 243 cardiomyopathy is inherited, establish the inheritance pattern, identify at-risk family members,

244 and provide information on disease characteristics within the family (e.g., age of onset, severity,
245 phenotypic variability within the pedigree, and treatment response). Reduced penetrance,
246 defined as individuals possessing a pathogenic variant but not manifesting any evidence of
247 disease, and variable expressivity is not uncommon in cardiomyopathy. For this reason a family
248 history of at least three generations is needed to determine the pattern of inheritance (dominant,
249 recessive, X-linked, mitochondrial).²⁸ Family history of more distantly affected relatives may be
250 informative regarding the pattern of disease within the family, through increased numbers of
251 affected individuals in the data set.

252 The writing group strongly recommends placing the family history into a graphical
253 pedigree format to enhance genetic competency for data interpretation, managing family-based
254 clinical screening, determining the mode of inheritance, facilitating the assessment of relatives
255 at risk, and for family counseling.²

256 Most cardiomyopathies presenting in adulthood are inherited in an autosomal dominant
257 manner. Cardiomyopathy presenting in childhood is also frequently inherited as an autosomal
258 dominant condition, but is more likely to have autosomal recessive, X-linked or mitochondrial
259 inheritance than in adults. *De novo* variants may be found in children or adults. In children, *de*
260 *novo* variants are most commonly identified for autosomal dominant and X-linked syndromic
261 cardiomyopathies. A child may be the first individual in a family to come to attention with a
262 primary HCM, DCM, or ARVC, and have a negative family history. Studies have shown *de novo*
263 events in up to 1/3 of cases with a negative family history, however cardiomyopathy may also
264 occur due to inheritance from an affected but asymptomatic parent unaware they have
265 disease.^{29, 30}

266 Assumptions regarding paternal or maternal transmission should be avoided, as bilineal
267 inheritance of autosomal dominant cardiomyopathy (transmission of disease from both mother
268 and father) can occur and may incur more severe and earlier onset disease. Compound or
269 digenic heterozygous variants classified in earlier studies have been shown in up to 5% of HCM

270 and up to 20% in ARVC patients,³¹⁻³³ although a re-evaluation of the previously published HCM
271 double variants applying the 2015 ACMG approach⁹ indicated double pathogenic or likely
272 pathogenic double variants were much less common.³⁴ Reliable data for DCM are not yet
273 available but also may be prevalent.³⁵ If the inheritance pattern can be established, accurate
274 risk assessment of relatives can be provided. While some digenic conditions have been clearly
275 established,³⁶ well-designed rigorous studies investigating di- or multigenic inheritance for the
276 cardiomyopathies are needed.

277 A family history provided by patients is frequently inadequate and may miss familial
278 cardiomyopathy.³⁷ Details from patients regarding heart disease in their family may be lacking,
279 and vague terms such as “heart attack” or “stroke” may be used for any sudden or unexplained
280 death. Ideally family history should be obtained from the most informed family member. Similar
281 to medical history, family history is dynamic and should be updated at regular intervals. Specific,
282 focused questions should be asked to ensure affected relatives are identified. Key elements
283 include: 1) cardiovascular symptoms (e.g., shortness of breath, paroxysmal nocturnal dyspnea,
284 or dyspnea on exertion), or symptoms suggestive of arrhythmia, including palpitations,
285 presyncope or syncope with or without exercise; 2) cardiovascular diagnoses such as
286 cardiomyopathy, heart failure or valve disease, or prior procedures including cardiac
287 catheterization, arrhythmia ablation, cardioversions, heart surgery, heart transplant, or use of
288 pacemakers or implantable cardioverter defibrillators (ICDs); all of these should include age at
289 time of symptom onset, procedures, or death; 3) sudden death, particularly under age 40, with
290 special attention to single vehicle accidents, drowning, or sudden infant death; 4) previous
291 genetic testing; 5) specific details on deaths attributed to “heart attack”; and 6) features of
292 syndromes, especially any features suggesting skeletal muscle disease. Also, if applicable; e.g.
293 short stature and learning problems suggesting Noonan, acroparesthesias and renal failure
294 consistent with Fabry or skeletal myopathy.

295 A critical component to validate family history often includes obtaining medical records
 296 and/or post mortem reports. Obtaining a family history and related activities outlined are time
 297 and effort intensive. Alternatively, focused family history interviews can be accomplished by
 298 trained allied health professionals. Practitioners may choose to refer patients with
 299 cardiomyopathy to centers expert in genetic cardiomyopathies, to obtain detailed family
 300 histories, provide genetic counseling and genetic testing, compile clinical and genetic
 301 databases, and provide opportunities to participate in research studies that are essential for
 302 progress in the field.

303 As noted above (Introduction, Supplementary Material), left ventricular noncompaction
 304 (LVNC) observed in conjunction with HCM, DCM, ARVC or RCM follows guidelines for that of
 305 the associated subtype of cardiomyopathy. If isolated noncompaction is identified
 306 serendipitously in an individual who is otherwise normal (asymptomatic with a normal ECG and
 307 normal ventricular size and function), it is always reasonable to obtain a family history to ensure
 308 there is no evidence of cardiomyopathy in the family, although formal population-based family
 309 studies of such individuals have not been published. Please see additional discussion at
 310 Guidelines 2 and 4.

311 **Guideline 2. Clinical (phenotypic) screening for cardiomyopathy in at-risk first-**
 312 **degree relatives is recommended.**

313	Cardiomyopathy Phenotype	Level of Evidence
314	Hypertrophic cardiomyopathy (HCM)	A
315	Dilated cardiomyopathy (DCM)	A
316	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	A
317	Restrictive cardiomyopathy (RCM)	A
318	Cardiomyopathies, overlapping, or extra cardiac	A
319	Left ventricular noncompaction (LVNC)	see background

320

321 **Key Points:** Cardiomyopathies are frequently clinically silent for extended periods of time.
322 Thus, first-degree relatives may be reportedly unaffected, and cardiomyopathy can only be
323 detected by clinical testing (denoted hereafter as “phenotype screening”). Relatives who
324 complete phenotype screening with no evidence of disease are denoted as “clinically
325 unaffected.” Relatives who are asymptomatic but have not completed phenotype screening are
326 denoted hereafter as “reportedly clinically unaffected.” Development of disease is age
327 dependent, thus assessments of at-risk relatives may require repeated phenotype screening.

328

329 **a. Baseline phenotype screening is recommended for all at-risk first-degree**
330 **relatives, including those who have tested negative for a known familial variant. (Level of**
331 **Evidence = A)**

332 The rationale for baseline phenotype screening for at risk family members is that, as
333 noted above, cardiomyopathy is commonly clinically silent and can only be detected by clinical
334 screening. The rationale for phenotyping family members who test negative for a familial variant
335 known to be actionable (i.e., pathogenic or likely pathogenic) is because in some cases non-
336 segregation (an individual with the cardiomyopathy phenotype who tests negative for a
337 pathogenic or likely pathogenic variant in the pedigree) will be unmasked, thus prompting the
338 need for expanded genetic evaluation. We also note that determining whether a variant of
339 uncertain significance (VUS) identified in the proband segregates with cardiomyopathy in a
340 family can only be accomplished with up-to-date clinical phenotype information in all at-risk
341 members of the pedigree. Furthermore, many variants continue to be novel for the
342 cardiomyopathies (the exception being for some variants in *MYH7* and *MYBPC3* where larger
343 numbers of pathogenic variants have been identified in HCM³⁸) and thus if only observed in the
344 proband will likely be assigned as a VUS, whereas knowledge of other affected family members
345 who also carry a variant initially assigned as a VUS may enable its reclassification to likely

346 pathogenic or pathogenic, which can then be used for predictive testing. For these reasons we
347 advocate that baseline clinical phenotype screening be conducted for all at-risk family members
348 in conjunction with initial cascade genetic testing of a family's disease-causing variant or
349 variants. Please see Guideline 3 for comments specific to children.

350

351 **b. Serial phenotype screening for cardiomyopathy is recommended in clinically**
352 **unaffected, at-risk relatives who are known to carry one or more disease-causing**
353 **variants. (Level of Evidence = A)**

354 Serial screening means, following a baseline-screening event, regular and repeated
355 phenotype screening events are then conducted over a period of years.

356

357 **c. Serial phenotypic screening for the emergence of cardiomyopathy is**
358 **recommended for clinically unaffected at-risk first-degree relatives whose genetic status**
359 **is unknown. (Level of Evidence = A)**

360 An unknown genetic status can occur when an at-risk individual has not yet been tested
361 for a previously detected disease-causing variant in the family, or if no pathogenic or likely
362 pathogenic variant has been identified in the proband. It can also occur if a VUS has been
363 identified in the proband and the family-based or other data are insufficient to allow
364 reclassification as a likely pathogenic variant.

365

366 **d. Serial screening of clinically unaffected relatives who have negative genetic**
367 **testing for a pathogenic variant is not recommended. (Level of Evidence = A)**

368 This recommendation is based upon the certainty that the variant identified in a family is
369 indeed pathogenic and is discussed below at [Guideline 4](#). However, relatives should be
370 counseled to present for evaluation if they develop signs or symptoms suggestive of disease.

371

372 **e. Clinical phenotype screening is recommended. (Level of Evidence = A)**

373 Clinical phenotype screening (Table 1) includes:

- 374 • Medical history, with special attention to heart failure symptoms, arrhythmias,
375 presyncope or syncope, and thromboembolism.
- 376 • Physical examination.
- 377 ○ Special attention should be given to cardiac and neuromuscular systems.
 - 378 ○ Examination is indicated of the integumentary system when ARVC is
379 suspected.
- 380 • Electrocardiogram.
- 381 • Cardiovascular imaging. This includes, minimally, a two-dimensional trans-thoracic
382 echocardiogram (2D-TTE) for all cardiomyopathies, augmented with tissue Doppler
383 interrogation, if available, for HCM. Cardiac MRI is rapidly emerging as a definitive
384 imaging modality; it should be used if echocardiographic imaging is inadequate or
385 equivocal. Additional studies may be considered based on the type of
386 cardiomyopathy and/or if symptoms are present.

387

388 **f. Suggested Clinical Screening Intervals for At-Risk Family Members.**

389 Clinical screening intervals are suggested (Table 2).

390

391 **Guideline 2 - Background.**

392 Cardiomyopathies span all ages – from prenatal to the elderly. The approach to clinical
393 phenotype screening of family members always relies on cardiac electrical, structural and
394 functional evaluations, with age- or phenotype-specific additions as needed. An ECG and an
395 echocardiogram are usually foundational in the initial phenotype screening for all ages of at-risk
396 pediatric and adult first-degree relatives.

397 Integration of the considerations given above, most importantly the type of
398 cardiomyopathy, should also be taken into account in screening of children. While children,
399 even neonates, do manifest cardiomyopathy, most disease is adolescent- or adult-onset. Hence
400 these recommendations should be integrated with the type of cardiomyopathy, the age of onset
401 of other affected members in the pedigree when such data are available, the identity of the
402 cardiomyopathy gene, if known, and other features. Additional guidance for the evaluation of
403 cardiomyopathy in pediatrics is covered in the next section.

404 Adult-onset cardiomyopathies commonly show variable expressivity, a variable age of
405 onset and reduced penetrance. Clinical screening of first-degree relatives of adults diagnosed
406 with cardiomyopathy is indicated, regardless of whether a disease-causing variant has been
407 identified in the index patient. In cases where first-degree relatives are all clinically unaffected, it
408 is reasonable to initiate genetic testing in the affected patient since identification of a previously
409 known disease-causing variant could lead to cascade testing in first-degree relatives. Because
410 of the variable age of onset, clinical screening repeated at intervals is recommended, even if
411 clinical genetic testing has not identified a disease-causing variant in the proband.

412 The risk for developing HCM after 50 years of age is reduced but not eliminated³⁹ as is
413 that for ARVC after age 50.⁴⁰ The favorable utility and role of Holter monitoring in the diagnosis
414 of ARVC has been reviewed.⁴⁰ Magnetic resonance imaging is useful for the diagnosis of ARVC
415 in centers experienced in its use and interpretation for ARVC;⁴¹ data are not yet available to
416 guide the frequency of its application for screening at-risk family members.

417 As noted above (Introduction, Supplementary Material), LVNC may be observed in
418 conjunction with other cardiomyopathy phenotypes, and if so, recommendations for that
419 cardiomyopathy drive clinical screening recommendations. We lack data on whether, in the
420 setting of normal ventricular size and function, the LVNC phenotype foreshadows the later
421 development of a specific cardiomyopathy or other forms of cardiovascular disease in an
422 extended pedigree. This is because the present literature of family-based screening has been

423 derived from LVNC identified at referral centers, in most cases in the setting of other
424 cardiovascular disease.⁴²⁻⁴⁴ Large systematic population-based studies to identify individuals
425 with the LVNC phenotype but otherwise with normal cardiac morphology and function, followed
426 by studies of their family members have not been done, although limited preliminary data are
427 available.^{42, 43} Because of the high prevalence of the LVNC phenotype in otherwise normal
428 individuals in population-based studies,^{19, 20} the limited evidence of disease causation from the
429 LVNC phenotype itself, and the limited individual and pedigree natural history data from
430 population-based studies, we provide no recommendations regarding family-based phenotype
431 screening of LVNC that is not accompanied by other cardiovascular phenotypes with known
432 disease risks.

433

434 **Guideline 3. Referral of patients with genetic, familial or other unexplained forms**
435 **of cardiomyopathy to expert centers is recommended.**

436

437 **a. Infants and children with cardiomyopathy should be evaluated by clinicians with**
438 **specific expertise in the recognition and testing of syndromic and non-syndromic**
439 **presentations of cardiomyopathy in this age group.**

440

441 **Key Points:** Expert centers are those with expertise in the evaluation, diagnosis and
442 management of genetic heart disease. Core competencies of expert centers include expertise
443 with cardiovascular phenotypes as well as the conduct of genetic evaluations. Such centers
444 should also have expertise in adults and/or children, dependent upon the ages of patients
445 referred. Especially for infants and children, this includes clinicians who are able to recognize
446 and characterize syndromes, dysmorphology, and metabolic abnormalities. Personnel at expert
447 centers include physicians who are board-eligible or board-certified in cardiovascular disease,

448 working collaboratively with genetics professionals, including genetic counselors and/or clinical
449 geneticists, ideally with cardiovascular expertise.

450

451 **Guideline 3 - Background.**

452 This recommendation is based on the marked genetic heterogeneity observed in
453 cardiomyopathy, the increasingly complicated interpretations of human DNA variation, and the
454 syndromic associations with some forms of cardiomyopathy. As noted below, both pre- and
455 post-test genetic counseling should be provided by a healthcare professional who is board-
456 eligible or board-certified in genetic counseling or clinical genetics, ideally with specialty training
457 and experience in cardiovascular genetics. Although all healthcare professionals are expected
458 to have core competencies in genetics, most cardiovascular providers do not have specific
459 training or certification in clinical genetics or genetic counseling.² The 2009 HFSA practice
460 guideline in genetic evaluation of cardiomyopathy acknowledged the challenges of obtaining a
461 family history.¹ The 2013 ACC/AHA guidelines also highlight the importance of obtaining at least
462 a 3-generation family history in the evaluation of cardiomyopathy.⁶ However, the genetic
463 evaluation of cardiomyopathy is more complex than identification of a familial pattern of disease.
464 This includes expert phenotyping to guide test selection and rigorous interpretation of genetic
465 testing results. Also, one recent study of genetic testing in clinical practice cited problems with
466 incorrect or inappropriate ordering, errors in analysis, incorrect interpretations, and incorrect
467 follow-up regarding VUSs, potentially jeopardizing patient safety.⁴⁵

468 In contrast with other subspecialty areas in cardiovascular disease, no consensus or
469 formal definition of the requirements for expertise in cardiovascular genetics is currently
470 available. Some training programs in Advanced Heart Failure and Transplant Cardiology or in
471 Cardiac Electrophysiology include genetics exposure, but typically training is insufficient to
472 achieve expertise to conduct an independent cardiovascular genetic evaluation. Similarly,
473 training programs in Clinical Genetics typically provide exposure to diagnostic evaluation of

474 cardiomyopathy, but may not provide sufficient training or experience in the recognition,
475 management and risk stratification of the heterogeneous cardiac phenotypes found in this
476 patient population. Clinical practice in cardiovascular genetics requires that practitioners remain
477 up to date with the wide range of genes in which pathogenic variants cause cardiac phenotypes,
478 including various forms of cardiomyopathy, arrhythmia, and syndromes in which these
479 cardiovascular manifestations occur. For these reasons the ideal construct includes a close
480 collaboration of specialists in both fields.

481 Because of the genetic and phenotypic heterogeneity inherent among different forms of
482 cardiomyopathy, a single healthcare provider is unlikely to be able to provide expert care alone.
483 Often, the range of expertise required is best achieved with a team of personnel who have
484 complementary training and experience, as a multidisciplinary approach is frequently essential
485 for optimizing diagnosis and management.^{2, 46, 47} Often a board-eligible or board-certified
486 genetics professional will work in conjunction with clinicians who are board-eligible or board-
487 certified in Cardiovascular Disease, pediatric, adult or both. One or more members of an expert
488 team involved with evaluation of cardiomyopathies may have subspecialty certification in
489 Advanced Heart Failure and Transplant Cardiology, and/or subspecialty certification in Cardiac
490 Electrophysiology. The evaluation of genetic heart disease includes whole families, so expert
491 centers ideally have teams of physicians and counselors who are experienced with providing
492 care for both adults and children with genetic forms of heart disease. Expert centers should be
493 able to advise patients properly about patterns of inheritance, family members who are at risk of
494 developing genetic heart disease, and reproductive risks related to variants in genes involved
495 with cardiomyopathies.

496 Although referral to an expert center is recommended for genetic evaluation of patients
497 with familial or otherwise unexplained forms of cardiomyopathy, the practicality of this
498 recommendation varies regionally. Travel to an expert center for genetic evaluation of
499 cardiomyopathy may not be feasible for some patients and their families. Additional options

500 through telephone-based genetic counseling and telemedicine-based genetic evaluation may
501 help in part to address this shortcoming.⁴⁸

502

503 **The Evaluation of Cardiomyopathy in Children Requires Special Expertise:**

504 Cardiomyopathy in children presents a unique differential diagnosis list, as compared to
505 adults, and geneticist evaluation may be required as syndromic and metabolic causes of
506 disease represent a higher proportion in children than in the adult population.^{49, 50} This is
507 particularly relevant in patients with intellectual disability of unknown etiology. Other extra-
508 cardiac findings that should prompt further evaluation and referral include dysmorphic features,
509 short stature, congenital anomalies, muscle weakness, or sensory deficits of unknown etiology.
510 Age at presentation may greatly aid in refining the differential list, with a specific set of disorders
511 more common in infancy. While there are many conditions that may cause cardiomyopathy in
512 childhood (see Supplemental Table for examples), a few are notable for having specific, time-
513 critical treatments available, or because the identification of the cardiomyopathy in the presence
514 of other findings may solidify the diagnosis of a specific syndrome. A number of conditions can
515 be screened by relatively inexpensive and rapid biochemical tests, followed by genetic testing
516 for a molecular diagnosis.

517 Aside from neuromuscular disorders, inborn errors of metabolism, and specific
518 syndromes noted in children, the same causes of familial HCM and DCM common in adults are
519 also encountered throughout childhood.⁵¹

520 Equally, syndromes with cardiomyopathy as a component may not be diagnosed until
521 adulthood, and thus syndromic cardiomyopathies should also be part of the differential
522 diagnosis among adults. In some cases, the dysmorphic features that form an integral part of
523 the diagnosis in infancy and childhood may not be as prominent later in life.

524 **Infancy.** Inborn errors of metabolism (IEMs) constitute an important group of conditions
525 that may manifest early in life. While expanded newborn screening may identify potentially

526 affected individuals, false negatives and missed screening confirmations can occur. Not all
527 diseases are screened in all jurisdictions, and some conditions are not currently amenable to
528 screening. Disorders of energy metabolism in particular should be considered: these may
529 present as either HCM or DCM, and include fatty acid oxidation defects (eg. very long-chain
530 acyl-CoA dehydrogenase [VLCAD], carnitine palmitoyl transferase 2 [CPT2], long-chain 3-
531 hydroxyacyl-CoA dehydrogenase [LCHAD] deficiency) and mitochondrial oxidative
532 phosphorylation disorders. If suspected, acylcarnitine profile, serum amino acids, urine organic
533 acids, liver transaminases, serum lactate, and comprehensive metabolic profile are
534 recommended first line studies. HCM in infancy should always invoke investigation for infantile
535 Pompe disease (glycogen storage disease type II) by enzyme assay for acid alpha-glucosidase
536 deficiency as early diagnosis is crucial for successful treatment by enzyme replacement
537 therapy. Of note, HCM may also occur secondary to corticosteroid use in preterm infants with
538 respiratory distress syndrome^{52, 53} or maternal diabetes⁵⁴ and should resolve spontaneously.
539 Persistence of HCM more than 4 weeks after cessation of steroids or past 6 months of age in an
540 infant of a diabetic mother should prompt evaluation for other causes.

541 Some syndromes with cardiomyopathy may present in infancy. Noonan syndrome or
542 other RASopathies are the most common syndromes associated with HCM, and may have
543 extra-cardiac manifestations of short stature and dysmorphic features that may be subtle and
544 difficult to recognize. HCM occurs in up to 20-30% of cases, with half presenting prior to 12
545 months of life with a more severe hypertrophy that paradoxically may improve over time.^{55, 56}
546 This may be biventricular, or involve predominantly the right ventricle. HCM rarely newly
547 develops past age of 5 years.⁵⁷ Molecular testing for RASopathies gene panel testing may or
548 may not be included with sarcomeric HCM genetic testing panels.

549 **Childhood.** Cardiomyopathy due to IEM may present in early or late childhood, typically
550 in individuals previously diagnosed with a specific disorder who receive cardiac screening.
551 Examples include the amino acid metabolism disorders methylmalonic acidemia and propionic

552 acidemia, glycogen storage disease type III (or very rarely type IV), and mucopolysaccharidoses
553 (MPS). Occasionally these conditions escape diagnosis or are misdiagnosed.

554 Neuromuscular disorders may first manifest with DCM in childhood, and include
555 muscular dystrophies (dystrophinopathies, laminopathies, desminopathies,
556 sarcoglycanopathies, and other recessive and dominant limb-girdle muscular dystrophies) and
557 Friedreich ataxia. Myotonic dystrophy, Types I and II, also present with cardiomyopathy
558 although more commonly in adults, especially type II. Both types also have risk for conduction
559 system disease.⁵⁸ Mitochondrial disorders may also present primarily as symptomatic
560 cardiomyopathy throughout childhood. Finally, boys with early onset cardiomyopathy should be
561 carefully evaluated for Barth syndrome (skeletal myopathy, small size, cyclical neutropenia,
562 delayed puberty, 3-methylglutaconic aciduria), an X-linked condition due to pathogenic variants
563 in *TAZ*, which is important for mitochondrial function.⁵⁹ Mitochondrial disorders may exhibit HCM
564 (~60%) or DCM (~30%).⁶⁰

565 **Selected Syndromes with Cardiomyopathy.** Careful history and physical exam are
566 essential to identify possible extra-cardiac manifestations of syndromes which may change
567 investigation and management. It is estimated that up to 10% of children with cardiomyopathy
568 have an underlying genetic syndrome. Over 100 different syndromes have been described with
569 cardiomyopathy as a feature. While most are very rare, several occur with higher frequency and
570 should be considered in the differential diagnosis (see Supplemental Table).

571 Several syndromes present more commonly in childhood. Alström syndrome may
572 present with transient DCM in infancy and later reoccurrence of DCM or restrictive
573 cardiomyopathy in adolescence. Other features include visual impairment (due to cone-rod
574 dystrophy) with nystagmus, progressive sensorineural hearing loss, obesity and diabetes due to
575 insulin resistance. Danon disease, an X-linked condition due to pathogenic variants in *LAMP2*,
576 frequently manifests in early childhood.⁶¹ It resembles infantile Pompe disease with severe HCM
577 but less pronounced skeletal myopathy, and has additional problems of cardiac pre-excitation,

578 intellectual disabilities, and retinal pigmentary disease. The variability in extra-cardiac features is
579 not well understood. Female carriers may present with either HCM or DCM, most often in the
580 second or third decades. Severe HCM due to 5' AMP-activated protein kinase (AMPK)
581 deficiency encoded by *PRKAG2* leading to non-lysosomal glycogen accumulation may also
582 present in childhood, frequently with arrhythmias, heart block and Wolf-Parkinson-White.⁶²
583 Fabry disease, an X-linked disorder resulting from mutations in *GLA*, causes deficiency of
584 alpha-galactosidase. Fabry may present as early as adolescence with LV hypertrophy.
585 Manifestations of classic Fabry include extra-cardiac features of angiokeratomas, painful
586 acroparesthesias, corneal opacities, reduced sweating, and end stage renal disease due to loss
587 of enzyme activity (typically <1%). However, variants in *GLA* that leave some residual enzymatic
588 function may result in cardiac variant Fabry, which usually presents at 40 years and older, in
589 which left ventricular hypertrophy is identified with or without proteinuria and without other extra-
590 cardiac manifestations.⁶³ Early enzyme replacement therapy, particularly for males and severely
591 affected females of this X linked disorder, may slow progression of disease. Atypical forms of
592 Fabry include a cardiac variant consisting of HCM, arrhythmia and conduction abnormalities
593 without renal failure, neuropathy or skin findings and present at a later age.

594

595 **Guideline 4. Genetic testing is recommended for patients with cardiomyopathy.**

596

597 **a. Genetic testing is recommended for the most clearly affected family member.**

598

599 **b. Cascade genetic testing of at-risk family members is recommended for**
600 **pathogenic and likely pathogenic variants.**

601

602 c. In addition to routine newborn screening tests, specialized evaluation of infants
 603 with cardiomyopathy is recommended, and genetic testing should be considered.

604

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmic right ventricular cardiomyopathy (ARVC)	A
Restrictive cardiomyopathy (RCM)	B
Cardiomyopathies associated with other extra-cardiac manifestations	A
Left ventricular noncompaction (LVNC)	See background

613

614 **Key Points:** Genetic testing is recommended to determine if a pathogenic variant can
 615 be identified to facilitate patient management and family screening. The identification of at risk
 616 family members is critical because the first presentation may be sudden death. Cascade genetic
 617 screening identifies asymptomatic affected family members and clinically unaffected carriers of
 618 pathogenic variants.⁶⁴ Institution of therapy in asymptomatic affected individuals improves
 619 outcomes and decreases hospitalization and death due to heart failure.^{65, 66} Preliminary studies
 620 indicate that treatment of clinically unaffected carriers of pathogenic variants may improve
 621 outcome as well although larger studies are needed.⁶⁷ Genetic testing and cascade screening
 622 for HCM have been shown to be cost-effective in Australia and the United States.^{68, 69} The
 623 identification of a molecular cause may also lead to critical gene-specific cardiac or extra-
 624 cardiac management recommendations. For example, cardiac hypertrophy seen in *LAMP2*,
 625 *PRKAG2*, *PTPN11* and *RAF1* pathogenic variant carriers can represent a genocopy of
 626 hypertrophy seen with sarcomeric pathogenic variants; yet *LAMP2*, *PRKAG2*, *PTPN11* and
 627 *RAF1* patients have different clinical courses and management needs.^{70, 71} In sarcomeric

628 carriers, genotype status is associated with long term outcomes, including all-cause mortality.⁷²
629 ⁷³ In DCM, there is evidence for prognostication value of genetic testing⁷⁴⁻⁷⁷ and management
630 implications for specific genetic findings, such as consideration of ICD for primary prevention in
631 carriers of *LMNA* pathogenic variants.⁷⁸ In ARVC, ICD placement for primary prevention in
632 asymptomatic male carriers of a malignant pathogenic variant showed significant impact on
633 long-term clinical outcome.⁷⁹

634 Testing should ideally be initiated on the person in a family with the most definitive
635 diagnosis and most severe manifestations. This approach will maximize the likelihood of
636 obtaining diagnostic results and detecting whether multiple pathogenic variants may be present
637 and contributing to variable disease expression or severity. Please see Guideline 3 for
638 additional comments on specialized evaluation of infants and children.

639

640 **Guideline 4 - Background**

641 Nomenclature follows the ACMG approach⁹ for calling variants as pathogenic (P), likely
642 pathogenic (LP), variants of uncertain significance (VUS), likely benign and benign. The
643 indications for genetic testing include guiding patient management and facilitating family
644 screening and reproductive risk assessment.

645

646 **Test Selection: Genes and Gene Panels**

647 Since the 2009 HFSA guideline,¹ the number of genes known that harbor rare
648 pathogenic variants that cause cardiomyopathy has increased, the number of clinical
649 laboratories performing high volume cardiovascular genetic testing has expanded, and the
650 number, type, and technologies available for gene-based sequencing have been in constant
651 evolution. While the 2009 guideline suggested that “genetic testing should be considered,”
652 additional data on the importance of genetic testing for prognostication and management as well

653 as cascade screening and risk stratification of relatives support the current genetic testing
654 recommendation. Furthermore, the cost for most large genetic panels is substantially lower than
655 it was in 2009, with expectations for continued decline.⁸⁰ Nevertheless, genetic testing is
656 probabilistic in nature and interpretation of genetic variation will continue to be refined as
657 additional sequencing information becomes available from both affected and unaffected
658 individuals.

659 The rationale for level of evidence presented in this guideline is derived largely from the
660 published sensitivity of genetic testing. These guidelines do not address molecular testing in
661 prenatal, newborn screening or *in-vitro* fertilization settings.

662 We also note ongoing challenges of variant interpretation in non-Caucasian, non-
663 Northern European populations, as most genetic testing, and hence repositories of known
664 pathogenic variants, has previously been conducted principally in the Caucasian/Northern
665 European population. The recent development of very large population databases (e.g., ExAC,
666 <http://exac.broadinstitute.org>, or gnomAD, <http://gnomad.broadinstitute.org>) now provides
667 limited numbers of reference alleles from non-European cohorts, which has greatly assisted
668 variant interpretation. However, genetic test interpretation of variant alleles from ethnic groups
669 not represented or represented in low numbers in reference datasets become extremely
670 challenging, and must be approached with considerable caution.

671 A variety of resources are publicly available that provide additional relevant information
672 (e.g., GeneReviews, <http://www.ncbi.nlm.nih.gov/books/NBK1116>), on individual genes (e.g.,
673 Online Mendelian Inheritance in Man, <http://www.omim.org>), specific genetic variants and their
674 population frequencies (e.g., dbSNP, <http://www.ncbi.nlm.nih.gov/snp>; ExAC browser,
675 <http://exac.broadinstitute.org>; Genome aggregation database (gnomAD)
676 <http://gnomad.broadinstitute.org/>; exome variant server, <http://evs.gs.washington.edu/EVS> or
677 1000 Genomes, <http://www.1000genomes.org>), and information for the interpretation of these

678 variants (e.g., ClinVar, <http://www.ncbi.nlm.nih.gov/clinvar> and ClinGen,
679 <http://www.clinicalgenome.org>).

680 We also note that large insertion/deletion variants (e.g., > 25 nucleotides) and other
681 structural changes in DNA, referred to as copy number variants, in a preliminary study represent
682 < 1% of cardiomyopathy cases,⁸¹ although structural variants have received minimal
683 investigation in the cardiomyopathies and may have greater relevance than is currently
684 understood.

685 **Whom to test.** In order to yield the most conclusive, informative results, diagnostic
686 genetic testing is optimally initiated on a confirmed affected individual. Furthermore, as there are
687 sometimes multiple genetic variants contributing to disease in a single family, the testing should
688 ideally be initiated on the person who is most likely to harbor the disease-causing variant or
689 variants. This is frequently the individual in the family with the most severe disease and/or the
690 earliest disease onset. This is a well-established principle in clinical genetics, as selecting the
691 individual with the most evident disease increases the likelihood of finding a genetic cause. If
692 the ideal person for initiation of genetic testing in a family is unavailable or unwilling to proceed,
693 then comprehensive genetic testing should be considered for another affected family member.

694 **When to test.** The timing for ordering genetic testing in a patient with cardiomyopathy
695 has not been studied. Because results may guide management, we recommend genetic testing
696 at the time a new cardiomyopathy diagnosis is made, but it can be conducted at any time
697 following diagnosis. Education and counseling regarding genetic testing options are a key
698 component of the process. For those who have had genetic testing in the past, re-testing may
699 be appropriate if the previous testing produced negative or inconclusive results and the test's
700 detection rate has improved. This latter point is particularly relevant for DCM as the gene panels
701 have rapidly expanded (e.g., inclusion of *TTN*^{15, 82, 83} and others) and are anticipated to continue
702 expanding.

703 Genetic testing for the cardiomyopathies may best be viewed as continuously evolving,
704 as new genes, and hence larger panels with greater sensitivity, continue to emerge. Although
705 no data are available, we suggest that repeat genetic testing is reasonable if test sensitivity has
706 increased by 5-10%. An alternative approach is to tailor retesting if particular characteristics of
707 the patient's phenotype are consistent with a newly identified gene. Further, the genetics
708 provider involved in a patient's care should periodically revisit results as variants may be
709 reclassified over time.^{46, 84, 85} Such reclassification includes upgrading variants from VUS to
710 likely pathogenic or pathogenic, as additional probands and affected family members with the
711 phenotype of interest are found to carry the variant. Conversely, some variants, previously
712 considered pathogenic, are downgraded to a VUS, or likely benign or benign, as larger datasets
713 from expanded ethnicities become available.

714 **How to test.** With the development of next generation sequencing (NGS), panels
715 incorporating dozens of genes relevant to the phenotype have become the norm, as they are
716 technically feasible and less costly.⁸⁰ As a result, clinical genetic testing panels for these
717 disorders are changing rapidly. Molecular genetic testing for multiple genes using a multi-gene
718 panel is now the standard of practice for cardiovascular genetic medicine. Furthermore, multi-
719 gene panel genetic testing is recommended over a serial single-gene testing approach due to
720 the genetically heterogeneous nature of cardiomyopathy. Genetic testing and cascade
721 screening have been shown to be cost-effective.^{68, 69}

722 Large gene panels for cardiomyopathy may include genes that cause genetic syndromes
723 associated with cardiomyopathy (eg. Fabry disease, Danon disease, Alström syndrome),
724 neuromuscular conditions associated with cardiomyopathy (eg. limb girdle muscular
725 dystrophies) or metabolic conditions. These large gene panels have the advantage of increasing
726 the likelihood of identifying a molecular etiology, especially in patients with mixed phenotypes or
727 those who lack pathognomonic features.^{86, 87} Considerable overlap of genes among different
728 types of cardiomyopathy (and other phenotypes) is also well established (Supplemental Figure

729 1). Panels also increase the likelihood of identifying individuals who carry disease-causing
730 variants in multiple genes, and this knowledge is extremely important for appropriate targeted
731 testing of family members.

732 With larger gene panels, the likelihood of identifying a VUS increases in proportion to the
733 number of genes tested, increasing the complexity of the interpretation and genetic counseling.
734 Importantly, the strength of evidence for gene-disease pairs on current panels differs, with some
735 well-established genes having a wealth of information regarding disease-causing variants, while
736 more recently identified genes having much less information available. The latter case increases
737 the likelihood of a variant being classified as a VUS. The composition of gene panels varies by
738 testing lab. It is critical that the ordering physician has an understanding of the uses, benefits,
739 and limitations of specific test types in order to select the most appropriate test for their patient
740 (Table 4.1). Addition of *TTN* and *BAG3* to DCM panels increased genetic testing yield by more
741 than 10%,^{15, 82, 83} but for HCM, recent studies have shown that expanded panels do not currently
742 increase sensitivity.⁶⁹ Thus the decision to order a panel that includes a larger number of genes
743 should be based on the specifics of the patient's medical history, physical exam findings, and
744 family history.

745 **HCM.** The level of evidence for testing in HCM is based on studies showing a high
746 diagnostic yield of genetic testing in children and adults and prognostic value of genotype
747 status.^{30, 69, 72, 73, 88} HCM is considered a disease of the sarcomere, and variations in genes
748 encoding sarcomeric proteins, in which there is low tolerance for genetic variation, are common
749 causes.⁸⁹ The diagnostic yield of HCM testing is approximately 30-60% (Table 4.2). The yield of
750 testing is higher in individuals who have a known family history of HCM.^{69, 88} Pathogenic variants
751 in *MYH7* and *MYBPC3* account for approximately 80% of all cases for which a molecular
752 diagnosis is achieved.^{90, 91} Beyond sarcomeric genes, core genes to screen in patients with
753 HCM include *GLA*, *PRKAG2*, and *LAMP2*, as reviewed in the Background of Guideline 3.

754 Infants and children with HCM may require more specialized evaluation and diagnostic
755 testing as noted in Section 3 because of the rate of syndromic conditions and inborn errors of
756 metabolism associated with HCM at these ages.^{49, 50, 92} Consultation with a geneticist is
757 indicated.

758 **DCM.** Evidence indicates that clinical genetic testing can identify the cause of DCM in
759 families with autosomal dominant inheritance in approximately 25-40% of cases, whereas in
760 isolated cases of DCM, the yield of testing is commonly estimated at 10-25%.^{35, 93-95} Core genes
761 to be tested in individuals with DCM include genes encoding sarcomeric and cytoskeletal
762 proteins (Table 3), although DCM testing panels typically carry several dozen genes, some with
763 uncertain significance. In most cases, all HCM and ARVC genes are included in DCM panels
764 because of gene/phenotype overlap.

765 Protein-truncating variants in *TTN* (*TTN*tv) represent the most common genetic testing
766 finding in DCM, ranging from 10-20% of cases.^{15, 82, 83} While many commercial testing
767 laboratories will adjudicate all *TTN*tv's, whether singleton or familial, as pathogenic or likely
768 pathogenic, variant interpretation is challenging due to the large size of the gene and the
769 frequency of truncating *TTN* variants in reference populations.^{82, 83, 96, 97} Most studies have not
770 been family-based, where segregation could be evaluated, but some non-segregation of
771 *TTN*tv's has been identified.⁹⁸ Further, recent cardiac magnetic resonance data of normal
772 individuals from a population-based study showed a small but significant decrement in LV
773 function with *TTN*tv's in constitutive cardiac exons,⁹⁷ suggesting that in some cases a *TTN*tv
774 may function as a risk allele.

775 The *LMNA* gene is the second most commonly identified cause of DCM with a
776 diagnostic yield of 5.5%, and gene-specific management recommendations, reviewed below,
777 are available.^{99, 100} More recently identified genetic causes of DCM such as *BAG3*, a chaperone
778 regulator, and *RBM20*, a protein required for RNA splicing, identify novel molecular mechanisms
779 for disease^{101, 102}, and are each identified in approximately 2% of DCM cases. DCM is a

780 common complication of neuromuscular disease such as Duchenne or Becker muscular
781 dystrophy. Genetic testing is important in mothers of individuals with Duchenne or Becker to
782 determine carrier status because carrier females may develop DCM in the third to fifth decade
783 of life.¹⁰³ As in HCM, infants and children with DCM may require additional diagnostic genetic
784 evaluation.

785 **ARVC.** The genetic basis of ARVC was initially identified as a disease of the
786 desmosome.¹⁰⁴ Genetic testing of *PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, *TMEM43*, and *PLN* resulted
787 in a molecular diagnosis in 63% of patients who fulfilled Task Force criteria for ARVC.¹⁰⁵ Digenic
788 inheritance and compound heterozygosity are frequent¹⁰⁶ and, combined with decreased
789 penetrance that is a feature of ARVC, may significantly complicate genetic counseling. ARVC
790 overlaps with arrhythmogenic left ventricular cardiomyopathy, sometimes more broadly referred
791 to as arrhythmogenic cardiomyopathy.¹⁰⁷ This reflects genetic and phenotypic overlap among
792 these forms of cardiomyopathy. Accordingly, genetic testing for ARVC using a larger
793 cardiomyopathy panel may identify non-desmosomal genes with pathogenic variants. Similarly,
794 desmosome gene mutations have also been identified in patients diagnosed with DCM.¹⁰⁸
795 Exercise has a well-established role in the pathogenesis of desmosomal cardiomyopathies, and
796 recognition of a desmosome gene mutation can help to determine optimal exercise
797 recommendations.¹⁰⁹

798 **RCM.** Genetic causes of RCM continue to be identified, but because RCM is a relatively
799 rare form of cardiomyopathy, numbers remain limited. A recent study identified a pathogenic
800 variant in 60% of subjects, primarily occurring in genes known to cause HCM.¹¹⁰ Family
801 members were frequently identified with HCM or HCM with restrictive physiology. Cardiac
802 amyloidosis resulting from pathogenic variants in *TTR* needs to be differentiated from other
803 forms of RCM due to the age demographic in which this occurs, the slowly progressive nature of
804 this disease, and therefore different management strategies.^{111, 112} The *TTR* allele p.Val142Ile
805 (commonly referred to as Val122Ile based on nomenclature for the circulating protein after N-

806 terminal peptide cleavage) has been found in 10% of African Americans older than age 65 with
807 severe congestive heart failure.¹¹³ Substantial recent progress with amyloidosis, both in imaging
808 strategies, including cardiac magnetic resonance and pyrophosphate scanning, and therapeutic
809 interventions in ongoing clinical trials, provide new incentives for genetic diagnosis.¹¹⁴
810 Hemochromatosis is uncommon but easily excluded with iron studies, such as percent
811 saturation of transferrin, and if present can be treated with iron removal.¹¹⁵

812 **LVNC.** As noted above, the LVNC phenotype may be observed in conjunction with all
813 other cardiomyopathy phenotypes, so considerations related to genetic testing should always be
814 directed by findings of a cardiomyopathy (or other cardiovascular) phenotype.^{16, 116} Genetic
815 testing is not recommended when the LVNC phenotype is identified serendipitously in
816 asymptomatic individuals with otherwise normal cardiovascular structure and function.¹¹⁷

817 **Special Circumstances:** A genetic etiology should be considered and a genetic
818 evaluation conducted in cases of peripartum cardiomyopathy, as rare variants in genes known
819 to cause DCM have been identified in patients with peripartum cardiomyopathy,¹¹⁸⁻¹²⁰ and *TTN*
820 truncating variants are present at rates similar to those found in the DCM population.¹²⁰ In cases
821 of sudden death with an autopsy diagnosis of cardiomyopathy, genetic testing may facilitate risk
822 stratification of family members.^{121, 122}

823

824 **Interpretation of genetic testing.**

825 Genetic testing results are probabilistic rather than determinative, and thus rely on
826 strength of evidence, both for and against, of specific variants causing or contributing to
827 disease. New guidelines have attempted to standardize and increase the stringency of
828 interpretation, with greater clarity regarding the criteria for strength of evidence and the
829 weighting of multiple sources of information that need to be incorporated to arrive at the
830 interpretation.⁹ Despite this, the interpretations provided for a given variant may differ between
831 clinical genetic testing laboratories.^{123, 124} In addition, updates and revisions of the laboratory

832 interpretation may occur as more information is obtained from larger cohorts, sometimes leading
833 to re-issuing of a clinical report with changed interpretation by diagnostic laboratories.

834 Because of their probabilistic nature, results of genetic testing must always be
835 interpreted in the context of the patient's medical and family history.⁸⁵ For example, family
836 history information and the segregation of a putative disease-causing variant within the family
837 may be important information to guide clinical interpretation, especially in cases where novel
838 genetic variants are identified. Also, family studies have noted more than one pathogenic variant
839 in up to 10% of families with ARVC.¹²⁵ Two or more variants have been seen in 3-5% of HCM
840 cases,³¹⁻³³ particularly if onset is early or severe.³⁰ Although not reported systematically, digenic
841 inheritance has been suggested to occur at even higher frequency with DCM.³⁵

842 The diagnostic yield of genetic testing for each subtype of cardiomyopathy is much less
843 than 100% (Table 2) and a negative genetic test result (in this setting including VUS and likely
844 benign or benign variants) does not rule out a genetic cause. Such an uninformative result in a
845 proband simply indicates that the genetic testing performed was unable to identify the specific
846 cause of disease in the given family. In these circumstances, an uninformative genetic testing
847 result cannot be used for predictive, cascade genetic testing in unaffected relatives. Rather,
848 family screening using phenotypic evaluations is recommended (Guideline 2). Larger panels,
849 better coverage of the relevant genes, analysis for deletions, duplications, and rearrangements
850 in the genes of interest, or exome sequencing in families with multiple living affected individuals
851 may identify a genetic etiology.

852 Finally, the recent availability of and much greater focus on extensive genetic testing
853 panels should not diminish or distract from the critical importance of expert phenotyping of
854 patients and families, and the relevance of highly insightful phenotype and gene-variant
855 correlations. Current genetics practice suggests that results provided by molecular genetics
856 laboratories drive clinical decision making, specifically actionability, in a genetic evaluation. In
857 the Family Management section below, this guidance states that a VUS cannot be used for

858 predictive testing, which the writing group firmly supports. However, we acknowledge that
859 compelling clinical data, for example, the pre-genetic test specification of a disease gene highly
860 likely to harbor a disease-associated variant of interest, seldom impacts the clinician's decision
861 of whether a variant classified as a VUS by a laboratory report is actionable. More specifically,
862 cardiovascular genetics experts have become quite sanguine, for example, at specifying the
863 pretest likelihood of identifying a *LMNA* variant based upon phenotype and/or family data.
864 However, finding a novel missense or nonsense variant in any gene, even with such a pretest
865 specification, cannot be classified with current ACMG rules as likely pathogenic (or pathogenic),
866 and thus actionable, unless data regarding the same variant is available from multiple probands
867 and/or affected family members. While we propose no solution to this present conundrum, we
868 do acknowledge its existence. Efforts to accumulate extensive catalogs of expertly adjudicated
869 phenotype and variant information, such as the ClinGen effort,¹⁰ may eventually partially
870 mitigate this situation.

871

872 **Considerations of Family Management**

873 **Predictive Genetic Testing**

874 Risk stratification in family members is an important and valuable reason for genetic
875 testing. If a pathogenic or likely pathogenic variant is identified in the index patient initially
876 tested, opportunities emerge for the predictive testing of at-risk family members. As noted
877 above, variants of uncertain significance (VUS) are not useful to conduct predictive genetic
878 testing.

879 **Negative cascade genetic testing in an at-risk family member.** If genetic testing is
880 negative in an at-risk phenotype-negative family member for a pathogenic or likely pathogenic
881 variant present in the proband, that family member's risk of developing the cardiomyopathy is
882 substantially reduced. In this situation the need for serial phenotype screening after a baseline
883 clinical evaluation in such a genotype-negative family member in most cases is unnecessary,

884 and the family member can be discharged from serial clinical phenotype screening. However,
885 the strength of the recommendation to release a family member from ongoing interval
886 phenotype screening is based upon the strength of the evidence that the variant indeed is the
887 cause of disease in the family under care. In most cases this evidence must be assembled from
888 prior patients and families, usually in publicly accessible databases or the medical literature,
889 and/or from evidence gathered and assessed from the family under care. The family member
890 should be counseled that their risk has been substantially reduced, but is not reduced to zero,
891 with the caveat that if they develop relevant symptoms, phenotype screening should be
892 reconsidered because of the possibility that one or more yet undetected variants may be at play.

893 **Positive cascade genetic testing in an at-risk family member.** On the other hand, if a
894 pathogenic or likely pathogenic variant is identified in an asymptomatic, at-risk phenotype-
895 negative family member, the confidence is much greater to infer risk for that individual. They
896 should be counseled on the presenting signs and symptoms of the specific cardiomyopathy, any
897 associated reduced penetrance and variable expressivity, and the rationale and frequency of
898 the recommended clinical surveillance (reviewed at [Guideline 2](#)).

899

900 **Leveraging Family-based Segregation Information to Impact Variant Analysis**

901 Some variants detected with cardiomyopathy genetic testing will be novel, that is,
902 variants that have not been previously reported in publicly accessible databases, and will meet
903 other usual criteria for pathogenicity. However, even if the variant is of the type that is known to
904 be disease-causing and has occurred in a well-established gene associated with the
905 cardiomyopathy phenotype in the family, such novel variants will often be adjudicated as VUSs
906 because of lack of prior case or family data. In this circumstance, searching for segregation of
907 the variant in question with the cardiomyopathy phenotype in additional family members can
908 provide additional valuable information. Depending upon the size of the pedigree, the number of
909 individuals tested, and the genetic testing results, such information may help reclassify a variant

910 from VUS to pathogenic or benign. The ClinGen initiative¹⁰ proposes to rectify this issue by
911 aggregating all available disease-associated variants into ClinVar, a publicly accessible
912 database utilizing a standardized curation approach tailored after the ACMG/AMP
913 recommendations,⁹ and all professionals with any access to genetic data relevant to the
914 cardiomyopathies are urged to contribute to this important database. However, because of the
915 numbers of genes involved in the cardiomyopathies, many variants in the near term will likely be
916 curated as VUS's. For example, in one HCM study, the cardiomyopathy with the largest
917 disease-specific databases and where ~80% of pathogenic variants can be identified in two
918 genes, *MYPBC3* or *MYH7*, in one recent study 30% and 35% of variants were novel,
919 respectively, for these two genes. In other well established HCM genes 76% of variants were
920 unique.³⁸

921 The corollary of the above is that if the VUS does not segregate with affected family
922 members, the likelihood that the VUS is relevant for the family phenotype is reduced. However,
923 this analysis must encompass the growing reality of bilineal or multi-variant disease, which has
924 been postulated to be more common in DCM^{8, 35} and ARVC.¹²⁶

925 In most clinical situations, sequencing a VUS is not undertaken in family members who
926 have completed clinical screening and have been shown to be free of the phenotype (negative
927 clinical phenotype screening), as genetic information will not inform variant pathogenicity. One
928 important exception to this is parental sequencing to confirm the possibility of *de novo*
929 occurrence of a variant. A second exception to this includes sequencing older unaffected family
930 members, who are highly informative when assessing the penetrance of a variant. Application of
931 this principle depends greatly upon the age of onset of the phenotype in the family (infant,
932 pediatric, early adult, late adult), the clarity and severity of the phenotype, as well as the gene
933 involved and disease mechanisms.

934 Finally, as noted above, variant calls may change. The most problematic is when a previously
935 called variant, deemed pathogenic or likely pathogenic, is downgraded to a VUS. In this circumstance,

936 recommendations for the clinical surveillance screening of at-risk family members change. Most
937 importantly, a genotype-negative family member must now be counseled that they remain at risk for
938 the family phenotype, and hence need to re-engage in clinical screening. The proband and any family
939 members who tested positive for the variant, now downgraded to a VUS, must also be counseled that
940 future genetic re-evaluation may be appropriate. All clinicians participating in genetic evaluations must
941 be aware of the implications of changes in variant calls, and the family members should be counseled
942 regarding these possibilities during the initial genetic evaluation and the need for possible future
943 contact. Given the seeming recent increase in downgrading to a VUS, this highly impactful change in
944 variant status carries great potential for unintended clinical errors if not identified and communicated
945 effectively to the relevant family unit.

946

947 **Guideline 5. Genetic counseling is recommended for all patients with**
948 **cardiomyopathy and their family members. (Level of Evidence A)**

949

950 **Key Point:** Genetic counseling for cardiomyopathy may be offered by board-certified or board-
951 eligible genetic counselors, clinical geneticists, or in the absence of available genetics
952 professionals, by clinicians who have the required background, expertise and training. Genetic
953 counseling for cardiomyopathy includes review of medical records essential for phenotyping,
954 obtaining a pedigree, patient and family education, evaluating genetic testing options, obtaining
955 consent for genetic testing, facilitating family communication, and ordering and interpreting
956 genetic test results while addressing psychosocial issues.

957

958 **Guideline 5 - Background**

959 Genetic counseling facilitates understanding and adaptation to the impact of a genetic
960 condition at the medical, psychological, and the family level,¹²⁷ and is valued positively as an

961 essential service by both caregivers and patients.^{1, 46, 128} This service may be provided by
962 clinical geneticists, genetic counselors, or specially trained nurses. In the United States this is
963 performed mostly by genetic counselors, who are mid-level providers with a Masters level
964 training in gathering, interpreting, and communicating medical genetics information. Their scope
965 of practice also includes psychosocial assessment and support. Genetic counseling
966 conceptualizes the family as the unit of care, with a broadened focus including preventive care
967 for at-risk family members.

968 Genetic counseling is usually undertaken by genetic counselors and/or clinical
969 geneticists who are knowledgeable of the cardiovascular features of the type of cardiomyopathy
970 in question, or by cardiologists, adult or pediatric, who are expert in the cardiomyopathy in
971 question and are fluent in the content and nature of genetic counseling. Cardiologists with
972 special interest and expertise in genetic cardiomyopathies usually integrate genetic counselors
973 into their practice.

974 Genetic counseling is an essential component of the evaluation, diagnosis, and
975 management of the cardiomyopathies. Genetic counseling roles include review and gathering of
976 medical records essential for phenotyping, obtaining a family history (Guideline 1), educating
977 the patient and family regarding the disease transmission and family risks, evaluating genetic
978 testing options (Guideline 4), obtaining consent for genetic testing including discussing the
979 implications of positive, negative, or uncertain results, providing key information to other at-risk
980 family members as identified by the index patient, ordering testing, interpreting genetic test
981 results, as well as communicating results and their clinical implications, including screening
982 recommendations for family members (Guideline 2).

983 Counseling is also aimed to promote informed choices and adaptation to risk or
984 condition while exploring and addressing psychosocial issues, as they emerge. Addressing
985 family dynamics, which could potentially impact dissemination of genetic information to at-risk

986 family members, is an active area of focus in genetic counseling that may be aided by the use of
987 patient letters, educational materials, or other communication tools.

988

989 **Guideline 6. Focused cardiovascular phenotyping is recommended when**
990 **pathogenic or likely pathogenic variants in cardiomyopathy genes, designated for**
991 **reporting of secondary findings by the ACMG, are identified in an individual.**

992

993 a. **If a cardiovascular phenotype is identified as would be predicted by currently**
994 **available knowledge of the gene/variant pair, all usual approaches described in**
995 **this document for a genetic evaluation, including family-based approaches, are**
996 **recommended.**

997

998 b. **If no cardiovascular disease phenotype is identified in the individual,**
999 **recommendations for surveillance screening at intervals should be considered.**

1000

1001 c. **If no cardiovascular phenotype is identified in the individual, cascade evaluation**
1002 **of at-risk relatives may be considered, tempered by the strength of evidence**
1003 **supporting the pathogenicity of the variant, the usual age of onset of the**
1004 **gene/variant pair, and pedigree information (e.g., the ages of at-risk family**
1005 **members, other previously known cardiovascular clinical data in the pedigree,**
1006 **and related information).**

1007

1008 **Guideline 6 - Background**

1009 Across specialties genetic testing is moving towards use of large gene panels, whole
1010 exome sequencing, and potentially whole genome sequencing. These tests may be performed
1011 for a wide variety of indications and diseases that do not include a cardiac phenotype.

1012 Individuals who undergo genetic testing for a disease that does not involve the heart may have
1013 a genetic variant discovered that may predispose that individual to a cardiomyopathy. This
1014 discovery may occur in two ways: 1) the gene, known to confer risk from high penetrance
1015 variants that are medically actionable, may be **intentionally analyzed** as recommended by the
1016 American College of Medical Genetics and Genomics. Variants identified from intentional
1017 analysis are termed secondary findings. 2) A variant is **identified incidentally or accidentally**
1018 through the analysis of genes related to the original phenotype for which the test was
1019 performed. These are termed incidental findings.

1020 The ACMG has developed guidelines to manage secondary findings, which were first
1021 published in 2013⁴ and updated in 2016.⁵ The ACMG guidance directs the reporting only of
1022 Known Pathogenic (KP) or Expected Pathogenic (EP) variants,⁵ the former defined as
1023 “Sequence variation is previously reported and is a recognized cause of the disorder” and the
1024 latter as “Sequence variation is previously unreported and is of the type which is expected to
1025 cause the disorder.” These definitions were taken from the ACMG 2008 guidance for variant
1026 interpretation,¹²⁹ which was updated by the ACMG/AMP in 2015⁹ with modified nomenclature of
1027 “pathogenic” (P) and “likely pathogenic” (LP). The latter attributions (P, LP) are now nearly
1028 universally used in clinical genetic testing laboratories in the US. This nomenclature is also used
1029 in ClinGen^{10, 11}, the ClinGen Cardiovascular Clinical Domain Working Group,¹³⁰ and this
1030 guideline. Despite possible subtle differences of KP/EP and P/LP, since the P and LP
1031 attributions are used for the other specific numbered guidelines in this document, for simplicity
1032 and parsimony these attributions will also be used in this section.

1033 Thus, variants in the ACMG-listed cardiomyopathy genes (Table 3) that have been
1034 identified as secondary findings and adjudicated as P or LP are considered medically
1035 actionable. In those cases, cardiac phenotyping should be conducted in the individuals who
1036 carry those variants, assuming that the individual has not opted out of notification.

1037 Greater difficulty in determining whether a variant is medically actionable may occur for
1038 incidental findings reported by the diagnostic laboratory that fall outside the ACMG guidelines.
1039 Incidental findings may be classified as pathogenic, likely pathogenic, variants of uncertain
1040 significance, likely benign or benign, with specific criteria for the strength of assertion.⁹

1041 The single most important analysis for determining if a specific incidental finding is
1042 actionable rests on the strength of evidence for disease causality of the gene/variant pair.
1043 Identifying a variant in a gene previously observed in multiple cases or families, including at
1044 times functional data confirming a damaging effect, can have substantial evidentiary strength,
1045 and such variants may be able to be classified as pathogenic or likely pathogenic. Such
1046 evidence forms the basis of the ACMG recommendations and informs sections a, b, and c of
1047 this guideline. For HCM, where 80% of genetic cause, when found, is within two genes
1048 (*MYBPC3*, *MYH7*), a greater likelihood exists that prior case data may be available. However, in
1049 contrast to HCM, the gene ontology for DCM is much more extensive, as most genes contribute
1050 only a small fraction to the totality of known genetic cause, and many reported variants remain
1051 private. The number of genes considered relevant for ARVC is smaller than either DCM or
1052 HCM, but because it is much less common than HCM or DCM, many ARVC variants will also
1053 remain private. Overall it is likely that most cardiomyopathy variants identified as incidental
1054 findings, even those for HCM, will remain VUSs because of lack of prior data, or lack of the
1055 requisite genetic data to assess segregation in large and well phenotyped families with multiple
1056 affected individuals.

1057 Item C of this guideline suggests thoughtful and cautiously implemented, cascade
1058 clinical (phenotype) screening of putatively at-risk family members may be considered, even if
1059 the clinical phenotype screening was negative in the individual (proband) who completed
1060 genetic analysis. This statement recognizes the possibility that the proband may be younger
1061 than the usual age of onset of the cardiovascular phenotype. It also recognizes the utility and
1062 necessity of gathering clinical phenotype data in an extended family to help interpret the genetic

1063 information in cascade testing if phenotypes are encountered in the family members predicted
1064 by the gene/variant pair.

1065 We also recognize that at times a novel variant will be identified in an established, well-
1066 curated¹³¹ gene known to have other variants of high risk, and the variant will be recognized as
1067 the type that is expected to be pathogenic, but because it is novel it may be appropriately
1068 adjudicated as a VUS. In select situations within the context of expert evaluation described
1069 above (Guideline 3) and known limitations summing the integrated risk derived from molecular
1070 genetics and clinical knowledge of the gene/variant pair (Guideline 4), a personal and family
1071 history, pedigree analysis and phenotyping of the individual harboring such a VUS may be
1072 considered. The rationale for this comment results directly from the significant risk of morbidity
1073 and mortality noted above that may devolve from such cardiomyopathy genes and variants. If
1074 phenotype evidence is found to support a disease association in the individual, the remainder of
1075 these guidelines would become operative, including consideration of pedigree expansion to help
1076 establish or refute the pathogenicity of the variant, and to better discern the overall risk incurred
1077 to the individual and the family.

1078 A distinct limitation is that we are unaware of published outcomes data to support,
1079 validate, or refute the above guidance, which can only be considered as expert opinion. This
1080 emphasizes the need for well-designed rigorous studies examining outcomes of phenotyping
1081 and family studies following secondary or incidental findings of variants relevant for the
1082 cardiomyopathies.

1083

1084 **Therapy Based on Genetic Evaluation and Cardiac Phenotype**

1085 The clinical characteristics associated with variants in some disease genes, when
1086 integrated with pedigree data, may directly influence the overall assessment and clinical
1087 recommendations for a patient or family.

1088 One gene with substantial evidence fitting this situation is *LMNA*, which commonly
1089 presents with nonsyndromic cardiomyopathy in adult cardiology practice and is well known for
1090 progressive conduction system disease (first-, second-, or third-degree heart block), usually with
1091 supraventricular and/or ventricular arrhythmias prior to, during or soon thereafter. All of this may
1092 occur prior to or contemporaneously with early DCM. Because in the US the use of ICDs is not
1093 recommended until the left ventricular ejection fraction (LVEF) falls to less than 35%, patients
1094 with *LMNA* cardiomyopathy may have inadequate protection from life-threatening ventricular
1095 arrhythmias if the LVEF remains >35%.^{78, 132} For this reason a specific guideline was created for
1096 the 2009 HFSA guideline¹ and has been preserved (Guideline 9). Other DCM genes (e.g., *DES*
1097 or *SCN5A*, *FLNC* and other genes not yet identified) may also have prominent risk of lethal
1098 arrhythmia and may also benefit from earlier ICD use.¹³³ As noted above, arrhythmia or sudden
1099 cardiac death, may precede the development of cardiomyopathy, and may be the presenting
1100 feature.

1101 Other genes with mutations causing syndromic diseases involving cardiomyopathy that
1102 have clear therapeutic indications include *GLA*, which encodes alpha-galactosidase A, and
1103 *GAA*, encoding alpha-glucosidase. Deficiencies of these enzymes cause Fabry or Pompe
1104 disease, respectively. Both have protein replacement treatments that have been shown to be
1105 efficacious.^{134, 135}

1106 The rationale for conducting genetic evaluations for the cardiomyopathies rests on the
1107 concept that in most cases treatment interventions once clinical disease has been recognized
1108 can forestall progressive disease and/or anticipate and prevent complications of disease
1109 progression. Each cardiomyopathy type has its own considerations that exceed the scope of
1110 this genetics oriented document. However, even surveillance for common complications (e.g.,
1111 sudden cardiac death, either from brady- or tachy arrhythmias in progressive *LMNA*
1112 cardiomyopathy; atrial fibrillation in long standing HCM; onset of heart failure in previously

1113 asymptomatic but progressive DCM) can trigger appropriate interventions with drugs and/or
1114 devices to prevent or ameliorate disease, as reviewed below.

1115 The role and risks of exercise in cardiomyopathy, and questions regarding exercise
1116 limitation, are frequently raised by patients and families. These have been addressed in other
1117 guideline statements.¹³⁶

1118

1119 **7. Medical therapy based on cardiac phenotype is recommended as outlined in**
1120 **consensus guidelines. Level of Evidence = A.**

1121 Guidelines for the evaluation and management of patients with cardiomyopathy have
1122 been published for HCM,^{137, 138} DCM,^{6, 139-141} and ARVC.¹⁴² These guidelines provide
1123 comprehensive guidance for care of those who are presymptomatic (stage B heart failure) or
1124 have had the onset of symptoms (stage C or D heart failure). Guidelines for the clinical care of
1125 patients with RCM are not yet available. Controversy continues whether LVNC represents an
1126 anatomical phenotype or distinct cardiomyopathy, and even when observed no specific
1127 treatment is indicated other than for associated cardiovascular phenotypes, as reviewed above.
1128 A multi-society (ACC/AHA/HFSA) guideline update for management of patients with heart failure
1129 has recently been published.¹⁴⁰

1130

1131 **8. Device therapies for arrhythmia and conduction system disease based on**
1132 **cardiac phenotype are recommended as outlined in consensus guidelines. Level**
1133 **of Evidence = B.**

1134 In brief, ICDs are indicated for secondary prevention of ventricular tachycardia or
1135 ventricular fibrillation regardless of the type of cardiomyopathy or degree of ventricular
1136 dysfunction. The indications for ICDs for primary prevention of sudden cardiac death in patients
1137 with nonischemic cardiomyopathy with reduced ejection fraction of any etiology are summarized

1138 in guideline statements,^{6, 139, 143-145} even though some ICD trials excluded individuals with familial
1139 cardiomyopathy associated with sudden death.¹⁴⁶ Device therapy for arrhythmia should not rely
1140 exclusively on the presence of a P or LP gene variant but must be integrated into overall
1141 attributable risk. For DCM, ICD therapy is indicated in patients who have a left ventricular
1142 ejection fraction less than or equal to 35% and who are in NYHA functional Class II or III (class
1143 I, level of evidence B). Additional class II and III guideline recommendations¹⁴⁴ are provided in
1144 Supplementary Table 3.

1145

1146 **9. In patients with cardiomyopathy and significant arrhythmia or known risk of**
1147 **arrhythmia an ICD may be considered before the left ventricular ejection fraction**
1148 **falls below 35%. Level of Evidence = C.**

1149 Electrophysiological disease can be considered broadly as conduction system disease
1150 and arrhythmia. Please see the discussion above regarding *LMNA* cardiomyopathy, however
1151 this guideline applies to any genetic cardiomyopathy that presents or progresses to lethal
1152 arrhythmia or heart block prior to advanced LV dysfunction. Examples of other conditions
1153 include the myotonic dystrophies.⁵⁸ Conventional guidelines apply for symptomatic or pre-
1154 symptomatic conduction system disease regardless of other aspects of the patient's clinical
1155 situation.¹⁴⁴ Pacemakers are indicated for symptomatic bradycardia, high grade AV block
1156 regardless of symptoms, or for any other symptomatic conduction system disease. Pacemakers
1157 may also be considered to allow for the institution of disease-modifying therapy (e.g., beta-
1158 blockers) when limited by bradycardia or along with AV junction ablation to treat refractory atrial
1159 fibrillation with rapid ventricular response. In the setting of *LMNA* cardiomyopathy and other
1160 genetic conditions with similar risk profiles requiring pacemaker placement, the use of an ICD
1161 rather than a pacemaker has been previously recommended¹ and is supported by extensive
1162 literature documenting the risks of sudden cardiac death concurrent with conduction system

1163 disease requiring pacemaker placement.^{76, 78, 99, 100, 147-150} For a patient with reduced ejection
1164 fraction that is likely to require chronic ventricular pacing, placement of a cardiac
1165 resynchronization therapy device (e.g., CRT-D) should be considered.

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Table 1. Studies Recommended in Baseline Clinical Phenotyping.

Study	DCM	HCM	ARVC	LVNC	RCM
CK-MM ¹	X			X	
ECG	X	X	X	X	X
ETT ²		X			X ³
Holter monitoring		X	X		X
CMR ⁴	X	X	X	X	X
Metabolic disease screening ⁵	X	X		X	X

¹CK-MM is the MM band (skeletal muscle) fraction of creatine kinase and should be completed if syndromic or neuromuscular disease is suspected. ²ETT, exercise treadmill testing. ³In children.

⁴Cardiac magnetic resonance imaging (CMR) is recommended if echocardiography is insufficient to define the phenotype; this is relevant to assess the cardiac morphology and function for all of the cardiomyopathies, and the presence and degree of fibrosis inferred from gadolinium uptake. ⁵Additional screening tests are indicated for pediatric onset and select adult onset presentations, see Guideline 3.

Table 2. Suggested Clinical Phenotype Screening Intervals by Age and Cardiomyopathy for Unaffected First-Degree Family Members of Affected Individuals

Cardiomyopathy	0-5 years ²	6-12 years	13-19 years	20-50 years	>50 years
DCM	Annually with positive FDR ¹	1-2 years with positive FDR ¹	1-3 years	2-3 years	5 years
HCM	Annually with positive FDR ¹	1-2 years with positive FDR ¹	2-3 years	5 years	5 years
ARVC	Consider once with positive FDR ¹	5 years	1-3 years	2-3 years	3 years
RCM	Annually with positive FDR ¹	1-2 years with positive FDR ¹	2-3 years	3 years	5 years

¹Positive FDR means that the unaffected but at-risk family member has a first-degree relative with the phenotype of interest. These screening intervals apply to at-risk family members when genetic testing: has not been performed or is uninformative in the proband, or when it has identified a likely pathogenic or pathogenic variant in the at-risk family member.

²Although most DCM is adult-onset and most HCM is adolescent- or adult-onset, both occur in neonates and young children. ARVC is early adult- to adult-onset. Data are limited for RCM.

Table 3. Selected Genes in Association with Cardiomyopathy

	Core genes ¹	Estimates of genetic testing diagnostic yield	ACMG Secondary Findings Gene List	Metabolic Causes of Cardio-myopathy	Examples of Genetic Syndromes
HCM	<i>MYH7, MYBPC3, TNNT2, TNNC1, TNNI3, TPM1, MYL2, MYL3, ACTC1, ACTN2, CSRP3, PLN, TTR, PRKAG2, LAMP2, GLA</i>	30-60%	<i>MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA</i>	GAA (Pompe); Mitochondrial disease genes	RASopathies (e.g., Noonan syndrome, others); Friedreich ataxia
DCM	<i>TTN^c, LMNA, MYH7, TNNT2, BAG3, RBM20, TNNC1, TNNI3, TPM1, SCN5A, PLN</i> . For testing, all HCM, ARVC genes are recommended to be included.	10-40%		Mitochondrial disease genes	Muscular dystrophies; Alström syndrome
ARVC	<i>DES, DSC2, DSG2, DSP, JUP, LMNA, PKP2, PLN, RYR2, SCN5A, TMEM43, TTN²</i> ; consider full DCM panel	10-50%	PKP2, DSP, DSC2, TMEM43, DSG2, RYR2, SCN5A		Naxos syndrome; Carvajal syndrome
RCM	Consider HCM or DCM gene panel	10-60%			
LVNC	Use the gene panel for the cardiomyopathy identified in association with the LVNC phenotype	Unknown		Mitochondrial disease genes including <i>TAZ</i> in Barth syndrome	1p36 deletion syndrome; RASopathies

¹Core gene lists represent genes with the highest diagnostic yield and/or strongest evidence of the gene in association with the listed phenotype; the genes listed are not exhaustive and should be considered illustrative for the type of cardiomyopathy. Considerable overlap of genes between cardiomyopathy phenotypes is well established. Genes known to cause metabolic disease or genetic syndromes are often included in testing panels, but vary depending on the clinical laboratory. Gene lists therefore need to be reviewed carefully before ordering testing. Metabolic and genetic syndrome columns provide examples only and are not intended to be comprehensive. ²Only *TTN* truncating variants are thought relevant for cardiomyopathy.

1 **Appendix. Author Relationships with Industry and Other Entities**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership / Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witnesses
Ray Hershberger	The Ohio State University College of Medicine and Wexner Medical Center, Columbus, OH	Array Biopharma	None	None	None	None	None
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Paul F. Kantor	University of Alberta, Stollery Children's Hospital, Edmonton, AB. CANADA.	None	None	None	None	None	None
Kim L McBride	Nationwide Children's Hospital and College of Medicine, Ohio State University, Columbus	None	None	None	None	None	None

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Ana Morales	The Ohio State University College of Medicine and Wexner Medical Center, Columbus, OH	None	None	None	None	None	None
Matt Taylor	University of Colorado Denver	Array Biopharma, Guidepoint Global, Wellpoint Inc	GeneDx	None	None	None	None
Matteo Vatta	Indiana University, Indianapolis, IN and Invitae Corporation, San Francisco, CA	None	None	Invitae Corporation, San Francisco, CA	None	Invitae Corporation, San Francisco, CA	None
Stephanie M. Ware	Indiana University School of Medicine, Indianapolis, IN	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be possibly relevant to this document. These relationships were reviewed and updated in conjunction with meetings and/or conference calls of the writing committee during the document development process. A person is deemed to have a significant interest in a business if the interest represents ownership of $\geq 5\%$ of the voting stock or share of the business entity, or ownership of $\geq \$5,000$ of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.